LETTER TO THE EDITOR

Reply: Infantile Leigh-like syndrome caused by SLC19A3 mutations is a treatable disease

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Sir,

The letter by Haack et al. (2014) provides important information confirming the role of the thiamine transporter hTHTR2 in Leigh syndrome and the beneficial effect of biotin and/or thiamine treatment for patients harbouring mutations in the gene encoding hTHTR2, SLC19A3. In recent years many new pathogenic mutations have been reported in SLC19A3 resulting in several age-related neurological phenotypes like biotin-responsive basal ganglia disease (BBGD), Wernicke-like encephalopathy and Leigh syndrome and various responses to biotin and/or thiamine (Zeng et al., 2005; Kono et al., 2009; Debs et al., 2010; Yamada et al., 2010). The exact mechanism by which biotin and/or thiamine treatment results in alleviation of the phenotype or prevents further disease progression is still unclear, but the current data challenge the initial hypothesis that biotin-induced upregulation of hTHTR2 could not explain the beneficial effect of biotin treatment in our patients with nonsense mutations (Gerards et al., 2013). A key role for thiamine was more likely and we proposed that the high amounts of thiamine administered would trigger an alternative transporter. We suggested the SLC19A2-encoded hTHTR1 as a possible candidate. Therefore, we did not propose an effect of biotin on SLC19A2 expression, as suggested by Haack et al. (2014), but on SLC19A3 expression. We agree with Haack et al. on the presence of an alternative transporter, but are not convinced that this could not be the SLC19A2-encoded hTHTR1. It has been proposed that high doses of thiamine might induce a biochemical change in hTHTR1, increasing the capacity for thiamine transport (Debs et al., 2010). In that way hTHTR1 could compensate for the hTHTR2 defect. Further functional studies should elucidate this issue.

Although treatment with biotin and/or thiamine alleviates the phenotype and prevents further disease progression in patients with SLC19A3 mutations, it is too early to conclude that these are fully treatable disorders. The patient reported by Haack et al. (2014) is still an infant and the beneficial effect of the thiamine treatment in the long-term has yet to be shown. Moreover, our patients received thiamine (100 mg/kg/day), and in one case also biotin (5 mg/kg/day), in infancy, but nevertheless died from the consequence of the SLC19A3 mutations in the second decade of life. More studies are warranted to illustrate the long-term effect of treatment with biotin and/or thiamine in case of SLC19A3 mutations, the mechanism in which they work and

in these studies and put forward by Haack et al. (2014) that the combination of biotin and thiamine is most effective.
whether additional environmental or genetic factors play a role in the efficiency of biotin and/or thiamine treatment. Nevertheless, current data clearly illustrate the benefits of biotin and/or thiamine in patients with SLC19A3 mutations, at least in the short term. Therefore, patients with suspected thiamine transport deficiency should be pre-emptively treated with both biotin and thiamine. It makes sense, as Haack et al. stress, to also do this in uncertain cases, where a genetic diagnosis still has to be established.

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### References


